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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,709	SIPPEL ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 24-83* is/are pending in the application.

4a) Of the above claim(s) *25,37,38,45,46,48-59,61-73,82 and 83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,24,26-36,39-44,47,60 and 74-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 1, and 24-83 are pending in the application. Claims 25, 37, 38, 45, 46, 48-59, 61-73, 82, and 83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 2, 5, 6, 9, 10-24, 26-36, 39-44, 47, and 60 were rejected in the prior action, mailed on August 12, 2003. In the Response, filed on January 12, 2004, the Applicant cancelled claims 2-23; amended claims 1, 24-35, 39-41, 43, 48, 51, 55, and 59; and added new claims 71-83. Claims 1, 24, 26-36, 39-44, 47, 60, and 74-81 are under consideration.

It is noted that claim 46 was indicated as rejected in certain 112 rejections in the prior action. However, this claim reads on non-elected subject matter as was only mistakenly included in the lists of rejected claims. The claim has not been examined on the merits and is withdrawn from consideration as to a non-elected invention. The office apologizes for any inconvenience.

Specification

2. **(Prior Objection- Maintained)** In the prior action, the specification was objected for lacking the section s required by #7 CFR 1.77. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use. The Applicant's attention is also directed to 37 CFR 1.77 (c), which states:

(c) The text of the specification sections defined in paragraphs (b)(1) through (b)(11) of this section, if applicable, should be preceded by a section heading in uppercase and without underlining or bold type.

The guidelines suggested as the preferred layout are as follows:

TITLE OF THE INVENTION.
CROSS-REFERENCE TO RELATED APPLICATIONS.
STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
BRIEF SUMMARY OF THE INVENTION.
BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
DETAILED DESCRIPTION OF THE INVENTION.
CLAIM OR CLAIMS (commencing on a separate sheet).
ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate amendment of the specification is required.

3. **(Prior Objection- Maintained)** The content of the present application's specification is objected to. In the application, the Applicant has included a number of Figures. However, there is no section of the specification providing the reference to, and brief description of, the drawing(s) as set forth in 37 CFR 1.74. Correction of the Specification is required.

Drawings

4. **(Prior Objection- Withdrawn)** New corrected drawings were required in this application for the reason indicated in the Form PTO 948 mailed with the prior action. The

submission of New Drawings with the Response is noted. These drawings are acceptable to the Examiner.

Claim Objections

5. **(Prior Objections- Withdrawn)** Claims 5 and 18 were objected to because informalities in the claim language. In view of the cancellation of these claims, the objection is withdrawn.

6. **(Prior Objection- Withdrawn)** Claim 41 was objected to because there was no article preceding the term "fusion protein" in line 2 of the claim. In view of the amendment of the claim, the objection is withdrawn.

7. **(Prior Objection- Withdrawn)** Claim 43 is objected to for informalities in the claim's preamble. In view of the amendment of the claim, the objection is withdrawn.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. **(Prior Rejection- Withdrawn)** Claims 1, 2, 5, 6, 9, 18-24, 26-29, and 60 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In view of the amendments to the claims, which indicate that the cell comprise a fusion proteins of a Ras polypeptide with an adaptor polypeptide, a construct which is not found in naturally occurring cells, the rejection is withdrawn.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. **(Prior Rejection- Withdrawn)** Claims 1, 2, 5, 6, 9, 18-24, 26-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims were rejected because it was unclear if the claimed cells were required to comprise effector and adaptor proteins, it was unclear if the parenthetical reference to adaptors was a limitation on the other proteins or polypeptides or an example of such other polypeptides or proteins, and because the language was contradictory in that it first indicated that the presence of an adaptor protein or polypeptide is optional, then required the presence of the effector in the form of a fusion protein comprising an adaptor. In view of the amendments to the claims, the rejection is withdrawn.

12. **(Prior Rejection- Maintained)** Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims were rejected because it is not clear what pathways are included by the phrase "Ras-like." Claims 2, 5, 6, and 18-23 have been cancelled, and claims 1, 24, and 26-29 have been amended such that they no longer refer to Ras-like signal pathways. Thus, the rejection withdrawn as to these claims.

The Applicant traverses this rejection on the grounds that the term "ras-like" would have been understood in the art, and points to Schlessinger, TIBS 18:273-75 in support of this

assertion. However, the reference merely teaches various pathways and components of such pathways in which the Ras protein is involved. The reference does not discuss ras-like pathways or provide any examples of proteins or pathways that could be identified as ras-like. Because neither the art nor the Applicant has provided any means of identifying a ras-like signal pathway, the indefiniteness rejection is maintained against claims 30-36, 39-44, 47, and 60.

13. **(New Rejection-Necessitated by Amendment)** Claims 30-36, 39-44, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on compositions or methods of using the cell of claim 1, wherein the cell includes a "ras or Ras-like signal pathway). However, claim 1 has been amended such that it requires the presence of a "constitutively active human ras polypeptide," thereby indicating that the cells within claim 1 are limited to those in which the signal pathway is a ras signal pathway. The rejected claims, by further including ras-like signal pathways, therefore appear to exceed the scope of what is included by claim 1, the claim from which they depend. Because these claims include subject matter excluded by the independent claim, it is not clear what the scope of these claims is. I.e., it is not clear if the claims are limited to ras signal pathways as indicated by claim 1, or if the claims may also include ras-like signal pathways. Clarification is required.

14. **(Prior Rejection- Withdrawn)** Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention. Claim 1 has been amended to require that the effector polypeptide is a constitutively active ras polypeptide. In view of the amendment of the claims, the rejection is withdrawn.

15. **(Prior Rejection- Withdrawn)** Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the cancellation from the claims of reference to a mediator section, the rejection is withdrawn.

16. **(Prior Rejection- Withdrawn)** Claims 18-24 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the cancellation of claims 18-23, and the amendment of claim 24, the rejection is withdrawn.

17. **(Prior Rejection- Withdrawn)** Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the language defining the claimed product wherein the "cell is a eukaryotic cell and, in particular, a yeast cell, specifically a yeast cell lacking cell walls." In view of the amendment of the claim to remove the rejected claim language, and clarifying a particular scope for the claimed invention, the rejection is withdrawn.

18. **(Prior Rejection- Withdrawn)** Claim 28 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it was unclear whether the cell itself was immobilized to a solid carrier, or if the cell is being applied to a solid carrier to which a number

of test ligands have been bound. In view of the amendment to the claim indicating that the former is the case, the rejection is withdrawn.

19. **(Prior Rejection- Maintained)** Claim 41 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim read on methods for identifying receptor ligands comprising contacting the claimed cells with a test substance "employed as fusion protein comprising a presumed ligand domain." The claim has now been amended such that it reads on an assay wherein the "test substance is employed as a fusion protein comprising a ligand domain capable of binding to said receptor." It is not clear what is meant by the phrase "employed as a fusion protein." The phrase could be interpreted either as defining the structure of the test substance, or as indicating that the test substance is inserted into the cell as used as the fusion protein described in the claims from which claim 41 depends. Clarification is required.

20. **(New Rejection- Necessitated by Amendment)** Claims 1, 24, 26-36, 39-44, 47, 60, 74-78, 80, and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on transformed cells, and compositions and methods relating to such cells, comprising " a human epidermal growth factor type membrane receptor." It is unclear what "type" of receptor is being referred to. I.e., it is unclear what characteristics of a receptor make it a human epidermal growth factor type membrane receptor. The Applicant has not

provided a definition by structure, function, or a combination of the two such that those in the art would be apprised of what constitutes a receptor of the indicated "type."

21. **(New Rejection- Necessitated by Amendment)** Claims 80 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on the cell of claim 1 "wherein the fusion protein is coded for a nucleic acid." It is unclear what is meant by this limitation. It appears that the claim should read on a cell wherein the fusion protein is encoded by a nucleic acid. Clarification is required.

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. **(Prior Rejection- Maintained)** Claims 1, 2, 5, 9, 18-24, 26, 27-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant cells wherein the Applicant has inserted a heterogeneous receptor into the cell, does not reasonably provide enablement for cells wherein the inserted receptors comprise portions of two or more receptors (e.g. the ligand binding domain of one receptor, and the transmembrane/cytoplasmic domain of another). The rejection of cancelled claims 2, 5, 9,and 10-23 is withdrawn as moot. The remaining claims have been amended to read on embodiments

wherein the cells comprise a "human epidermal growth factor type membrane receptor." As indicated above, it is not clear what receptors, other than human EGF receptor, fall within the scope of the claimed genus. Because the scope of the claims is unclear, it is assumed that the claims still read on hybrid receptors as were rejected in the prior action.

The Applicant appears to be traversing the rejection by arguing that the Applicant has provided sufficient teachings regarding the making and use of the claimed inventions. Response, pages 20-21. However, while the Office agrees with the Applicant's reading of the law, the Applicant has provided no more than an assertion that that the specification is enabling for the claimed inventions. In short, the Response provides only an unsupported conclusion that the specification is enabling.

Argument by the attorney does not replace evidence. See e.g., MPEP 2145, and In re Geisler, 43 USPQ2d 1362 (CAFC 1997). While the discussions in these reference are primarily concerned with arguments in rebuttal of obviousness rejections, they nonetheless demonstrate that naked argument on the part of the Applicant is insufficient, without support, to overcome a prima facie rejection of the claims. In the present case, the Applicant provided no evidence in traversal of the arguments and teachings in the art cited by the Office in the prior action. Rather, the Applicant has provided only a blanket assertion of enablement without even addressing the particular grounds of rejection posed by the prior action. In view of the lack of a specific ground of traversal of the rejection, and a failure of the claim amendments to overcome the rejection, the rejection is maintained over claims 1, 24, 26, 27-36, 39-44, 47, and 60, and extended to new claims 74-78, 80, and 81 for the reasons of record.

24. **(Prior Rejection- Maintained)** Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain cells and assays does not reasonably provide enablement for the elected invention wherein the receptor is a tyrosine kinase receptor, or to embodiments wherein the receptors' mediator section is associated with any tyrosine kinase, and the adaptor protein is a protein capable of binding an alpha unit of a G-protein (a Gα protein). It is noted that the claims have been amended such that they no longer include reference to embodiments wherein the adaptor protein is a protein capable of binding a Gα protein. However, the claims are broad enough to read on embodiments including any adaptor proteins, including those wherein the adaptor protein binds a Gα protein. Because the Applicant elected such embodiments, and therefore indicated such embodiments were encompassed by the claims, and because the Applicant has not excluded such embodiments from the claims, the rejection is maintained against claims 1, 24, 26-31, 34-36, 39-44, 47, 60, and against new claims 74-81.

25. **(Prior Rejection- Maintained)** Claims 1, 2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims described a genus of inventions wherein any Gα binding protein may be used as an adaptor protein for use in targeting an activated Ras protein to the plasma membrane of a cell by binding to a tyrosine kinase receptor mediator section. Applicant's traversal regarding the distinction between the cDNA of Eli Lilly, and the cells and proteins of the present case is noted. The traversal appears to be on the grounds that the current rejection is concerned with genera of proteins, while those of Eli Lilly were concerned with DNA. This is

not found persuasive in the court nowhere indicated that the legal considerations stated in the decision were limited to cases wherein the technology under consideration was limited to DNA. Further, the Applicant indicates that the pending claims were drawn to recited classes of proteins known in the art, and therefore the Applicant was in possession of them. However, the rejection was not on the basis that either tyrosine kinase receptors or Gα binding proteins were not known in the art, but that they were not known to associate directly with one another. The Applicant has not pointed out any examples in the application or in the art that such an association is known; therefore, the Applicant has not demonstrated possession of the claimed genus of inventions regardless of the knowledge of the two groups of proteins in the art. The rejection is therefore maintained against claims 1, 24, 26-31, 34-36, 39-44, 47, 60, and against new claims 74-81.

26. **(Prior Rejection- Withdrawn)** Claims 1,2, 5, 6, 9, 18-24, 26-31, 34-36, 39-44, 47, and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments of the claimed invention wherein the claimed cell comprises an active Ras protein, does not reasonably provide enablement for embodiments of the claimed invention wherein effector region of the effector protein comprises a Ras protein other than an active member of the Ras family. In view of the amendment to the claims, which require that the fusion protein include an active Ras protein, the rejection is withdrawn.

27. **(Prior Rejections- Withdrawn)** Claim 5 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, and as failing to comply with the written description requirement. The claim read on a class of cell comprising any fusion protein of any adaptor and effector, wherein the fusion protein requires enzymatic modification

in order to become operative. The claim was rejected because the Applicant has not provided any written description by which those in the art could identify members of the claimed genus; the Applicant has not met the written description requirement for that genus of inventions. In view of the cancellation of the claim, the rejection is withdrawn.

28. **(Prior Rejection- Withdrawn)** Claim 18 was rejected in the prior action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim read on embodiments wherein the mediator protein of the claimed cell receptor is bound to several adaptor proteins although there does not appear to any written description support for such an embodiment in the application. In view of the cancellation of the claim, the rejection is withdrawn.

29. **(New Rejection- Necessitated by Amendment)** Claims 1, 24, 26-36, 39-44, 47, 60, 74-78, 80, and 81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection. Claim 1 has been amended to read on transformed cells comprising "a human epidermal growth factor type membrane receptor." However, while the specification describes cells comprising human epidermal growth factor (EGF) receptors (page 2, lines 14-20), the specification does not appear to provide support for a genus of inventions comprising human EGF *type* receptors. Rather, the specification indicates that the EGF receptor is an example of a type of receptor identified as an enzyme-coupled receptor, and does not indicate

that the EGF receptor is itself a type of receptor. Because the application does not provide support for a genus of human EGF type receptors, a genus of receptors comprising human EGF receptor, the amendment to the claims referring to such a genus of receptors appears to be New Matter to the application. The Applicant is required either to cancel such subject matter from the claims, or to point out where support for the rejected subject matter lies in the application as filed.

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. **(Prior Rejection- Withdrawn)** Claims 1, 2, 6, 9, 18-24, 26, 27, 30, 35, 36, 42, 43, 44, 47, and 60 were rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Trueheart et al., U.S. Patent 6,159,706. This rejection is withdrawn in view of the amendments to the claims, and the arguments in traversal which were persuasive. In particular, the claims have been limited to particular type of receptor and a particular effector protein, the particular combination of which is not suggested by the Trueheart reference.

32. **(Prior Rejection- Maintained and Extended)** Claims 1, 2, 6, 9, 18-21, 26, 27, 30, 35, 36, 39- 44, 47, 60, and claims 31-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart as applied to claims 1 and 30 (and others) above, and further in view of Ostanin et al. (U.S. Patent 6,251,605), and of Isakoff et al. (EMBO J 17(18): 5374-87), and Aronheim (Nuc Acids Res 25(16): 3373-74). The claims have been amended to read on embodiments wherein the receptor is an EGF type receptor and the effector polypeptide is a constitutively activated human ras polypeptide. The rejection is withdrawn as to claims 2, 6, 9, and 18-21, which have been cancelled from the Application. The rejection is maintained over the teachings of Trueheart in view of Ostanin, Isakoff, Aronheim, and further in view of Li et al. (J Biol Chem 272(16): 10337-10340) and Baldari et al. (J Biol Chem 267(7): 4289-91) against amended claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, and 60, and extended to new claims 74, 75, 77-81.

The Applicant traverses the rejection on the grounds that the indicated references do not teach or suggest the claimed cell including the fusion protein of a constitutively active RAS with an adaptor protein. The Applicant argues that the reference do not provide motivation or reasonable expectation of success in the combination. The traversal is not found persuasive.

The teachings of the references were described in the prior action. In particular, Trueheart was described as teaching the following:

> The patent teaches that, where a heterologous receptor is provided, the preferred embodiment also includes the inactivation of the homologous receptor (native to the cell). Col. 15, lines 13-15. Further, the reference teaches that the host cells for the heterogeneous receptor are cells wherein the receptor can activate a signal transduction pathway. Col. 15, lines 60-63. As an example of such a pathway, the patent discusses the yeast Ras pathway. Col. 16, lines 30-52.

Thus, the patent teaches the insertion of the heterologous receptors into the yeast cell such that they can activate the Ras signal transduction pathway. Each of Isakoff and Aronheim teaches the use of fusion proteins as adaptors to bypass deficiencies in cellular pathways, and indicate that

what is necessary for the activated Ras to signal its pathway is for the protein to localize the Ras to the plasma membrane. See e.g., Aronheim, page 3373 left column. In view of these teachings, it would have been obvious to those in the art that fusion of activated Ras to any compound that would localize the pathway inducer to the cellular membrane would be effective in activating the Ras pathway. Because Trueheart teaches the expression of heterologous receptors and the incorporation of such receptors into endogenous pathways, and particularly the Ras pathway, and because the Isakoff and Aronheim references teach methods of incorporating signals otherwise excluded from cellular pathways into the cell signal transduction pathways, it would have been obvious to those in the art to use fusion proteins such a those taught in these two references to incorporate the heterologous receptors of Trueheart into the yeast cell signal pathways. Further, the success demonstrated in each of the Isakoff and Aronheim references indicates that such a use of the fusion proteins is likely to be effective (i.e. demonstrates a reasonable expectation of success).

It is further noted that the Isakoff reference indicates that it is the activated Ras that is included in the fusion protein, and that it is known in the art that it is activated Ras that leads to activation of the signal pathways. See, Isakoff, abstract, and page 5376; and Aronheim, abstract. Further, because the teachings of Trueheart indicate that the assays for the heterologous receptors involve the activation of the ras pathway, it would be apparent to those in the art that it would be beneficial for the claimed cell to be operative in detecting ligands to the receptors for the Ras proteins to be active. It is known in the art that certain variants of ras are constitutively active, and that such forms of the protein can be incorporated into signal pathways. See, abstracts of each of Li and Baldari. Thus, because the methods of detecting cell ligand receptors of Trueheart

would involve the active forms of Ras, and because the Isakoff reference indicates that the active form of the protein is operable in the fusion protein disclosed, it would have been obvious to those in the art to use such constitutively active proteins in the cells disclosed by Trueheart.

The Applicant has provided neither arguments as to why the references fail to show motivation or reasonable expectation of success, not provide evidence to support their conclusion. Because the Applicant has merely made conclusory statements the references do not provide such motivation or expectation of success, the arguments are not found persuasive. The rejection is therefore maintained.

33. **(Prior Rejection- Maintained)** Claims 1, 2, 6, 9, 18-21, 26, 27, 31-33, 35, 36, 42, 43, 44, 47, and 60 were rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 31 above, and further in view of Pacifici et al., WO 94/29458 (Se also U.S. Patent 5,521,295). The Applicant has provided no further arguments in traversal of this rejection to those presented above. Because those arguments are not found persuasive, the rejection is maintained against pending claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, 60, 74, 75, and 77-81.

34. **(Prior Rejection- Maintained)** Claim 34 was rejected in the prior action under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 31 above, and further in view of Mitsuzawa et al. (Genetics 123: 739-48), and DeClue et al. (Mol Cell Biol 11(6): 3132-38). The Applicant has provided no further

arguments in traversal of this rejection to those presented above. Because those arguments are not found persuasive, the rejection is maintained

35. **(Prior Rejection- Maintained)** Claims 1, 2, 6, 9, 18, 22-24, 26, 27, 30, 31-36, 39-44, 47, and 60 were rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart, Ostanin, Isakoff, Aronheim, Li, Baldari, Mitsuzawa, and DeClue as applied above, and further in view of either Jiang et al. (Nature 395: 808-13), or Bence et al. (Nature 289: 296-99) and in light of the teachings of Kawakami et al. (J Immunol 16: 1785-802), and Rawlings et al. (Science 271: 822-825). The Applicant has provided no further arguments in traversal of this rejection to those presented above. Because those arguments are not found persuasive, the rejection is maintained against pending claims 1, 24, 26, 27, 30-36, 39-44, 47, 60, 74, 75, and 77-81.

36. **(Prior Rejection- Maintained)** Claims 28 and 29 were rejected under 35 U.S.C. 103(a) as obvious over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied against claim 1 above, and further in view of any of Ashby et al. (U.S. Patent 5,569,588) or Fink (U.S. Patent 5,532,157), and further in view of the Applicant's disclosure on pages 42, and 74. The Applicant has provided no further arguments in traversal of this rejection to those presented above. Because those arguments are not found persuasive, the rejection is maintained.

37. **(New Rejection-Necessitated by Amendment)** Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Ostanin, Isakoff, Aronheim, Li, and Baldari as applied to claims 1, 24, 26, 27, 30-33, 35, 36, 39-44, 47, and 60, and extended to

new claims 74, 75, 77-81 above, and further in view of Delorme et al., Appl Environ Microbiol 55(9): 2242-46. Claim 76 further limits the claimed inventions to embodiments wherein the host cell is a yeast cell lacking a cell wall. Delorme teaches that among the means for making transformation of yeast cells easier, one such method involves the removal of the cell wall. Page 2242, left column. Because the methods and cells of the other references indicated above involve the transformation of yeast cells, and because the Delorme teaches that a means of improving such transformation is to remove the cell walls, it would have been obvious to those in the art to use yeast cells whose cell walls had been removed in the construction of the indicated cells. Thus, the cumulative teachings of these references render obvious the claimed invention.

Conclusion

38. No claims are allowed.

39. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 4/2/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600